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FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP 901 NEW YORK AVENUE, NW WASHINGTON, DC 20001-4413			EXAMINER LUCAS, ZACHARIAH	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/561,345

Applicant(s)

KRUPKA, UDO

Examiner

ZACHARIAH LUCAS

Art Unit

1648

Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 August 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 24-42 is/are pending in the application.
- 4a) Of the above claim(s) 36-39 and 41 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 24-35, 40, and 42 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/S5108)
- Paper No(s)/Mail Date 3 lists.
- 4) ☐ Interview Summary (PTO-413)
- Paper No(s)/Mail Date _____.
- 5) ☐ Notice of Informal Patent Application.
- 6) ☐ Other: _____.

DETAILED ACTION

1. Claims 24-42 are pending in the application.

Election/Restrictions

2. Applicant's election with traverse of Group I, and the species represented by the election of residue 73 of SEQ ID NO: 12 in the reply filed on August 11, 1008 is acknowledged. The traversal is on the ground(s) that the common technical feature of the claimed inventions and species is SEQ ID NO: 12, and that dependent claims containing all of the features of an independent claim should be included in the same Group even if the claims contain a further invention. These arguments are not found persuasive.

First, it is noted that the common technical feature of the Groups is not SEQ ID NO: 12 itself, but is any polypeptide that comprises an amino acid sequence of at least 5 consecutive amino acids of that sequence, and comprises one of the amino acid positions of (e.g.) claim 28. As is indicated by the anticipation rejections below, this does not represent a special technical feature over the prior art. The argument that the different inventions share a common special technical feature is therefore not found persuasive as the common feature is not a feature which distinguishes over the prior art.

With respect to the argument that dependent claims containing all of the features of an independent claim should be included in the same Group even if the claims contain a further invention, it is noted that the referenced section of the PCT Annex (except that Applicant should refer to Annex B, not Annex A) indicates that this is the case where "the independent claims

avoid the prior art” and satisfy unity of invention. As indicated above, and in the restriction requirement, this situation does not apply in the present claim set.

Finally, Applicant asserts that there would be no serious search burden in the examination of each of the claimed inventions. This argument is not found persuasive. Each of the inventions is drawn to a distinct molecule, with a distinct structure and function, and requires separate sequence searches and search logic. Thus, there is burden in the co-examination of each of the claimed inventions.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 36-39 and 41 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on August 11, 2008.
4. Claims 24-35, 40, and 42 are under consideration.

Information Disclosure Statement

5. The information disclosure statements (IDS) submitted on December 20, 2005; and on March 8 and June 23, 2006, are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner.

Claim Rejections - 35 USC § 101

6. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claims 24-33 and 40 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. These claims are drawn to "[a]n oligopeptide or polypeptide comprising an amino acid sequence with at least 94% identity to SEQ ID NO: 13." The application teaches that SEQ ID NO: 13 is a fragment of the HBsAg protein from an HBV isolated from a patient. It is noted that the claims do not require that the oligopeptide or polypeptide is isolated or purified. Thus, the claims read on a protein comprising SEQ ID NO: 13, wherein the protein may be part of the indicated HBV virus. The claims therefore read on a protein that may be found in nature, and on the virus that is found in nature. The claims therefore read on non-statutory subject matter.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 28, 30-35, 40, and 42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 28 is treated as representative. This claim reads on a peptide comprising "at least 5 consecutive amino acids from SEQ ID NO: 12, and comprising at least one" of the indicated amino acid positions of that sequence. It is not clear from the claim language if the claim is requiring that the consecutive amino acid sequence from SEQ ID NO: 12 includes the indicated amino acid position, or if the claim is requiring a consecutive sequence

from claim 12, and an amino acid position corresponding to that identified amino acid positions. It is noted that one of the problems with the claim is further highlighted by the existence of both claim 28, which merely requires the presence of the amino acid position 73 of SEQ ID NO: 12, and of claim 31, which both requires that presence of the amino acid position, and specifies the amino acid to be found in that position. Through the inclusion of claim 31, which specifies the amino acid found at the position corresponding to amino acid 73, it is implied that any amino acid may be present in the amino acid position corresponding to amino acid 73 in the polypeptide of claim 28.

Moreover, it is not clear what is meant by the language requiring that the polypeptide comprises one of the indicated amino acid positions. For example, it is not clear if the claim is requiring that the polypeptide includes a position 73, includes a position 73 having the same amino acid that is found in position 73 of SEQ ID NO: 12, or if the polypeptide need only include the amino acid found in the position 73 of SEQ ID NO: 12.

Clarification of the scope of the claims is required.

10. Claims 25, 40, and 42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 25 is drawn to a genus of polypeptides comprising any polypeptide that is at least 94% identical to SEQ ID NO: 13 (a fragment of the Hepatitis B surface antigen-HBsAg from HBV variant HDB 05), and that retains the ability to bind to sera from individual

infected with HBV variant HDB 05. Claims 40 and 42 read on kits or methods for the use of polypeptides that are at least 94% identical to SEQ ID NO: 13 for the purpose of detecting antibodies against HBV. These claims therefore implicitly require that the polypeptides are capable of binding sera from HBV infected patients (or at least antibodies that bind to HBV).

The following quotation from section 2163 of the Manual of Patent Examination Procedure is a brief discussion of what is required in a specification to satisfy the 35 U.S.C. 112 written description requirement for a generic claim covering several distinct inventions:

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus... See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

It is also noted that even the presence of multiple species within a claimed genus does not necessarily demonstrate possession of the genus. See, *In re Smyth*, 178 U.S.P.Q. 279 at 284-85 (CCPA 1973) (stating "where there is unpredictability in the performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus or combination claimed at a later date in the prosecution of a patent application."); and *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, at 1405 (Fed Cir 1997)(citing *Smyth* for support). Thus, when a claim covers a genus of inventions, the specification must provide sufficient written description support for the entire scope of the genus. Support for a genus is generally found where the applicant has provided a number of examples sufficient so that one in the art would recognize from the

specification the scope of what is being claimed, or provided a function and a structure correlating with that function. However, in situations where the operability of other species than those provided is uncertain, additional support may be required over that which would be required where greater certainty is present.

In the present case, the Applicant has provided claims drawn to a genus of polypeptides having a sequence of at least 94% identity to SEQ ID NO: 13, wherein the polypeptides react with either HBV or HBV variant HDB 05 reactive sera. It is noted that the Applicant has indicated that the HCV protein comprising this sequence does not react with antibodies directed to other HBV variants. See, App., pages 9 and 42-43. In addition, the application also provides no examples of proteins, other than the sequence itself, which shares at least 94% identity to SEQ ID NO: 13, including no examples of such sequences that bind to antibodies directed against either HBV generally, or the specific HBV variant HDB 05. The application therefore indicates that SEQ ID NO: 13 itself does not react to anti-HBV antibodies generally, and fails to identify any variants of SEQ ID NO: 13 that bind to either anti-HBV or anti-HBV HDB 05 antibodies.

The teachings in the art indicate that single amino acid changes can alter the antigenicity of the protein. See e.g., Riffkin et al., Gene 167:279-83, abstract (indicating that a single amino acid change between two proteins determines the ability of such proteins to bind to an antibody). The art also indicates that amino acid substitutions outside of an antigenic site in a protein may affect that ability of the protein to react with antibodies targeting the protein. Abaza et al., J Prot Chem 11:433-44. Thus, the art indicates that there is uncertainty in the ability of mutant versions of proteins to interact with antibodies directed against the original protein.

In addition to the teachings of uncertainty relating to the ability of mutant proteins to react with antibodies directed to the unmutated protein, the teachings of the application further indicate the unexpectedness of the inability of the protein of SEQ ID NO: 13 to react with other anti-HBV HBsAg antibodies. See e.g., page 9. Thus, the teachings in the application and in the art indicate that there is significant uncertainty as to the ability of mutants of SEQ ID NO: 13 to react with antibodies directed to either HBsAg proteins comprising SEQ ID NO: 13 or to HBsAg proteins from other HBV variants.

In view of the uncertainty in ability of mutants of SEQ ID NO: 13 to perform the required functions (binding to anti-HBV or anti-HBV HDB 05 antibodies), and the lack of any disclosure of other species than SEQ ID NO: 13 that perform such functions, the disclosure fails to provide adequate support for the claimed genus.

It is noted that descriptive support may also be provided by the combination of a function with a correlating non-functional characteristic. However, the Applicant has not demonstrated that sharing 94% identity to SEQ ID NO: 13 is a structural characteristic that correlates with the ability of a protein to bind either of the indicated groups of antibodies.

The claims are therefore rejected as lacking adequate descriptive support for the claimed genus of polypeptide comprising mutants of SEQ ID NO: 13.

11. Claims 24, 26, 33-35, 40, and 42 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for polypeptides comprising SEQ ID NO: 13, does not reasonably provide enablement for the use of any polypeptide comprising an amino acid sequence of at least 94% identity to that sequence. The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

As indicated above, the claims broadly read on a genus of proteins comprising any protein of at least 94% identity to SEQ ID NO: 13. This genus comprises a large group of potential proteins. However, the only example of such proteins provided in the application is that of SEQ ID NO: 13 itself. Thus, the application provides only limited teaching with respect to mutants of SEQ ID NO: 13, and the uses which mutants of the protein may be applied.

The uses for which such proteins may be used depends on knowledge by those of ordinary skill in the art of the antigenicity of the proteins (i.e. the ability of such proteins to react with or induce anti-HBV antibodies), or of the protein to perform other functions known to be held by the HBsAg protein. However, as was indicated above, there is significant uncertainty in the ability of mutants of SEQ ID NO: 13, even those with as few as one amino acid change, to

interact with other anti-HBV HBsAg antibodies, or even with antibodies specifically directed to the HBsAg from which SEQ ID NO: 13 was derived.

Moreover, teachings in the art demonstrate that there is unpredictability in the art of protein modification generally, specifically in the effects of modifying protein sequences on the function of the protein. See e.g., Bowie et al., Science 247:1306-10. The teachings of the specification would indicate that this uncertainty is exacerbated with respect to the HBsAg protein comprising SEQ ID NO: 13 as this protein already appears to vary from the conformation and structure of other HBsAg proteins. This is demonstrated by the inability of antibodies directed to other HBsAg proteins to interact with the protein comprising SEQ ID NO: 13, wherein the antibodies are believed to bind conformational epitopes. App., pages 5 and 10. This is especially the case in view of the Applicant's admission on page 4 of the specification that "[n]ot all mutations result in replication-capable viruses and there is frequently coexistence with replication-capable virus..." Thus, while there is knowledge in the art regarding the structure of HBsAg proteins generally, it is not clear to what extent such knowledge specifically applies to SEQ ID NO: 13.

In view of the breadth of the claims, the limited provision of working examples and the limited disclosure regarding the structure and functional and antigenic properties of the HBsAg comprising SEQ ID NO: 13, and the uncertainty and unpredictability in the art, the indicated claims are rejected because there is insufficient information provided to enable those in the art to use the claimed polypeptides without undue experimentation.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 28 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Quinnan et al. (WO 00/07631). These claims are drawn to oligopeptides or polypeptide comprising at least 5 consecutive amino acids of SEQ ID NO: 12, and the amino acid of position 73 of SEQ ID NO:

12. For the purposes of this rejection, the claim is read as including any polypeptide comprising 5 consecutive amino acids of SEQ ID NO: 12, wherein the consecutive sequence includes an amino acid corresponding to position 73 of that sequence. The Applicant identifies the sequence of TRTST as such a sequence. See e.g., Response of August 2008, top of page 9.

Quinnan teaches a polypeptide comprising such a sequence. See, page 27(SEQ ID NO: 4 of the reference includes the sequence TRTST). The reference therefore anticipates the indicated claims.

14. Claims 28, 33-35, and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by Langley et al. (EP 0533492). These claims are drawn to compositions comprising a polypeptide comprising at least 5 consecutive amino acids from SEQ ID NO: 12, and comprising amino acid position 73 of SEQ ID NO: 12. In view of the indefinite claim language of claim 28 as described above, the claim is read as requiring that the claimed polypeptide includes a position corresponding to the identified position of SEQ ID NO: 12, but not necessarily requiring that the

same amino acid be found in that position. Claims 34 and 35 require the recombinant production of the polypeptide, and the purification of such from other polypeptides.

Langley teaches an HBsAg protein sharing at least 5 consecutive amino acids with SEQ ID NO: 12, and comprising an amino acid corresponding to position 73 of SEQ ID NO: 12. See e.g. Figure 1 (showing sequence encoded by SEQ ID NO: 1 of the reference), and claims 1-10. The reference also teaches the recombinant production and purification of the protein. Pages 6-7. The reference therefore anticipates the indicated claims.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

16. Claims 34 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Quinnan et al. (WO 00/07631- supra). These claims read on methods of recombinantly producing the peptides of claims 28 and 31.

As indicated above, Quinnan teaches peptides meeting the limitations of these claims. In addition, the reference also teaches that proteins and peptides of the invention may be prepared by any available means, including recombinant expression. Page 8. While the reference does not specifically teach such expression and isolation of the polypeptide of SEQ ID NO: 4 of that reference, it would have been obvious from these teachings to one of ordinary skill in the art that

such recombinant expression methods could also be used for this polypeptide. The reference therefore renders the claimed methods obvious.

Conclusion

17. No claims are allowed.
18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ZACHARIAH LUCAS whose telephone number is (571)272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Zachariah Lucas/
Primary Examiner, Art Unit 1648